

DATE: 19 August 1977

To : Joshua Lederberg

FROM : Howard Cann

SUBJECT: "Genetics Center" renewal deadline

Josh, This memo responds to your memo of August 5. I am in general agreement with your comments, especially those pertaining to the role of the "center" in providing knowledge which bridges basic science and chemical applications, the importance of creating an intellectual focus for genetics (this should be human genetics) in the medical school, the recruitment of new sub-projects from investigators not presently part of the program project grant and the distinction between a "Center" and a group of individual research grants. While I agree that we should stress new initiatives, I would suggest that our renewal application contain a mix of continued and new projects. I have reviewed the projects of the present "center" and I believe they have merits which qualify them for consideration for inclusion in the renewal application. Inclusion of some or all of these projects, perhaps with innovations, will enhance our chances of success.

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NIZAS.
The project on polymorphisms of binding proteins (Luca) has, I think, been successful. Polymorphisms of vitamin D and B₁₂ binding proteins have been described and studied for the first time. Now the work has turned to understanding the basic defect of cystic fibrosis and promising results have already been found. I have no hesitation in recommending inclusion of a cystic fibrosis research project (involving Luca and Giovanni Romeo) in the renewal application. The innovation here in applying the original approach to cystic fibrosis. This project certainly justifies the philosophy of the Center in that it bridges basic science and clinical applications.

Another center project which serves as a bridge is the use of the cell sorter (FACS) to isolate fetal cells from the maternal circulation. The clinical application here is prenatal diagnoses. The project has not been progressing as rapidly as anticipated, the problems essentially being serological, but recent results are encouraging. The project will appeal to the most critical of study sections. Should the promising results continue to emanate from the fetal cell - FACS project, and we will know by November - December, I would urge that this project be included in the renewal application.

What originally began as an investigation of gene markers in amniotic fluid in my laboratory has evolved over a 2 year period to human gene mapping, using somatic cell hybridization and family studies, of and within the HLA region. Genetics of HLA continues to be one of the most important and relevant scientific efforts in human genetics. Fortunately, at Stanford there is a world-recognized HLA group (Payne and McDevitt) and I have the opportunity to advise, consult and collaborate with this group. The

The finding of a balanced 5/6 translocation from our clinical cytogenetics lab has permitted us to initiate somatic cell hybrid experiments for localization of the HLA region on chromosome 6. We are close to confirming its localization to the short arm of chromosome 6, and we have the first somatic cell hybrid data demonstrating co-segregation of the HLA region and the locus for glyoxylase I (GLO) in hybrid clones. The family studies, performed in collaboration with the Stanford HLA group, involve typing families showing recombination within the HLA region for markers at loci within the region (HLA-A,B,C,D and Bf) and at a syntenic locus (GLO) at about 5cM (proximately toward the centromere) from the region. This is a form of fine gene mapping (certainly for man) which is establishing detailed order of genes within the HLA region. Our lab has provided the polymorphic Bf (properdin factor B, a serum protein which serves as a major component of the alternate pathway of complement activation) and GLO electrophoretic markers in these studies, and a highly informative recombinant individual for HLA-Band BF has been found. We have data on recombination between HLA A and C, and we are accumulating extensive data on recombination frequencies for loci within the HLA region. We have abstract for various aspects of these studies (V International Congress of Human Genetics, VII International Histocompatibility Workshop and the 1977 Somatic Cell Genetics Meeting) and I anticipate three of four published papers by the end of the center grant period.

I must put in a pitch for identification of the Stanford "Genetics Center" with HLA activities. McDevitt, Payne, et al. in Medicine and Immunology are probably going to be supported by a program-project immunogenetics grant (N.I.A.I.D.), but this does not preclude collaborative efforts between the individuals in the two "centers". As indicated above, a significant portion of my research is HLA-related and I hope to continue. I think it is appropriate for the "Genetics Center" to contribute to this research activity. If our "Genetics Center" is to "create an intellectual focus for genetics in the medical school"-- and I believe it must do so-- interaction with the HLA immunogenetics group is essential. Interaction need not pertain to active collaboration alone; joint seminars, joint teaching, joint clinical activities, graduate student rotation, etc. should be encouraged.

The project on the impact of genetic counseling in family decision-making (Cliff Barnett) deals with an important area of research. There apparently are very few active research projects attempting a behavioral analysis of genetic counseling. Similar projects (e.g. that of Roy Antley, a pediatrician in Indianapolis) are not as scientifically sound as the Stanford project. I think it most appropriate for the Center to continue support of this project, especially since it is so unique. Data are being collected and analyzed. Risk and burden, within the context of genetic counseling, are seen to be perceived "rationally" (i.e. as physicians and geneticists perceive them) by couples undergoing counseling, and an amazing retention of risk figures (and their meaning?) has been noted up to 8 months after counseling. One or two manuscripts are in draft form and there is an abstract of a presentation at the V International Congress of Human Genetics.

I shoulder much responsibility for the slow progress in the clinical aspects of the GC/MS project. No previously unrecognized disorders have been found by us. I gather, however, this is a familiar story for other GC or GC/MS units (e.g. Berkeley, UCLA, U.C. La Jolla) operating as we do. This, in part, must be a function of relatively small numbers of patients available for metabolic screening. We (Stanford) are not a center for metabolic diseases, although we, along with the other university medical centers and some other hospitals, have been designated such a center by the State Department of Health. Perhaps the way to go is to actually become such a center, building clinical activities around our GC/MS facilities, but other diagnostic facilities (e.g. clinical biochemistry and diagnostic enzymology) and service activities would have to be supported. While fee for service may eventually pay for a metabolic disease center facility, initial capitalization would be required. Incidentally, the State Department of Health has designated U.C.S.F. as the center for screening newborns for hereditary metabolic disorders in northern California, although there is no action yet because initial start-up funds are not available. Stanford wasn't interested in this purely service-oriented activity.

We have had some interesting experiences with the GC/MS project. We diagnosed methylmalonic acidemia in one infant (from Santa Clara Valley Medical Center), the diagnosis confirmed by (Yale and Leon Rosenberg) demonstrating complete deficiency of liver methylmalonyl CoA mutase after the patient died. Unfortunately, this inborn error of metabolism had been discovered and defined (in part by ~~W~~ellum) about 5 years ago. We confirmed the diagnosis of primary hyperglycemia in a newborn infant (also from Santa Clara Valley Medical Center) from GC/MS analysis of blood, urine and CSF. This diagnosis should be and was made by the amino acid analyzer initially. The use of GC/MS here permitted us to rule out other courses of hyperglycemia (such as propionic and methylmalonic acidemia). I do provide consultation for a moderate number of infants and children with classic PKU and hyperphenylalaninemia ("variants" of PKU) and the urine of some of these patients has been analyzed in detail by GC/MS in various therapeutic and diagnostic situations, e.g. before and after institution of dietary therapy and during initial challenge with phenylalanine loads. While the metabolite profile of PKU is well known (even N-acetylphenylalanine, which we identified in urine of a young infant with classic PKU before treatment, has been described), there may be some virtue in intensive metabolic study of the hyperphenylalaninemic variants. We have begun to analyze urine of such variants, but, again, the numbers of patients are small.

We are making progress on the GC/MS pattern of normal urine and amniotic fluid, important information for recognizing the abnormal situation. Thus far, there is not much progress (anywhere) in prenatal diagnoses by testing amniotic fluid for metabolite accumulations. I believe this has been performed once or twice (for methylmalonic acidemia and argininosuccinic aciduria) in conjunction with assays of the relevant enzymes in the cultured amniotic fluid cells. I believe we should make the effort to screen pregnancies at-risk for infants with hereditary metabolic disorders (again, the numbers are small), and I intend to contact U.C.S.F. (about 1,000 amniocenteses per year - Mickey Golbus) about a collaborative effort in this area.

I cannot begin to evaluate progress or automation (including automatic identification) of the GC/MS process. You are undoubtedly familiar with this aspect of the project.

Thus, Josh, I can find progress and merit in the "Genetic Center" programs, and some or possibly all (at reduced funding) should be included in our renewal package. I agree with the need to manifest innovation in the existing efforts that are to be continued. Furthermore, we should recruit new sub projects!

In the Genetics Department, Doug Wallace and Gan are potential contributors and/or collaborators. I think Doug can provide basic information pertinent to diseases which might, in part, result from abnormalities of mitochondria. Gan has the background, knowledge and motivation to contribute to our Center in (eukaryote--human would be nice) molecular cytogenetics. For instance, he is presently helping John Stone (Graduate Student in my lab) isolate the Barr Body! I don't know where you and Stan Cohen are with respect to applying recombinant DNA techniques to human genetics, i.e. to bridging basic science and clinical applications. There is no doubt about the enormous biological and eventual clinical significance of this work, and it can (almost) always be justified in various types of grant applications if the appropriate scientists are involved. The point I must make is that if a recombinant DNA project is included in the renewal application, it should unambiguously meet your criteria regarding clinical or at least human genetics applications.

Other department should be canvassed, and I am aware of relevant activities in some of them. The focus in Medicine should be HLA. Jack Barchas, Roland Ciaranello (child psychiatry), Tom Anders (Chief of child psychiatry) and I have been talking and reading together and generally interacting in an area that I like to think of as genetic basis for abnormal behavior. This interaction was initiated by a patient with the Lesch-Nyhan Syndrome (X-linked HGPRT-, self mutilation, etc.) for whom I am providing care. We have collaborated in two clinical Research Center protocols concerning treatment of this patient with 5-hydroxytryptophan and carbidopa (peripheral amino acid decarboxylase inhibitor) to ameliorate the self mutilation. Bill Nyhan and others have also undertaken such clinical investigations. In addition to the enormously beneficial therapeutic features of such undertakings, (incidentally, we were not successful in significantly cutting down the self mutilation), the biochemical-pharmacologic aspects may well help us relate, in detail, HGPRT deficiency to self mutilation. We have also been talking about applying our joint efforts to autism, but nothing much has been done so far. Our rejuvenated OB department does not have too much genetics activities at the moment. We were unable to pry Mickey Golbus away from U.C.S.F. Two new faculty (very good) perinatologists, Paul Hensleigh and Desmond McCallum, are collaborating with our clinical genetics program, providing amniocentesis services. Dr. Hensleigh is interested in investigating early amniocentesis as a cause of Rh isosensitization. The potential risk is there, and we have seen one Rh- woman become sensitized after (and presumably as a result of) the procedure. Questions pertain to the magnitude of the risk and prevention or sensitization. Should anti-D immune globulin be used during pregnancy? This important clinical investigative effort may qualify for our renewal application.

I have been continually frustrated in my efforts to find financial support of integrated clinical genetics activities at Stanford. There are three faculty level clinical geneticists at Stanford (Short, Luzzatti, and I), and we do provide various services for individuals with genetic disorders, birth defects and in need of genetic counseling. There are 4 clinics specifically involved with these clinical activities - genetic counseling, birth defects, genetics-metabolic and medical genetics. Laboratory support for clinical genetics has come from the clinical cytogenetics lab in Pediatrics (which I direct) and which is primarily oriented to chromosome analysis, and cell culture. We are clearly deficient in laboratory support for clinical biochemical genetics, and I am referring to diagnostic enzyme assays. We should have the capability at Stanford for performing assays of various lysosomal enzymes in white blood cells, fibroblasts, serum etc. on a fairly routine basis. Our present facilities are so lacking that it is difficult to pry time from my research assistant to isolate white blood cells for shipment to another center (e.g. U.C. San Diego) for diagnostic enzyme assay. Our clinic populations are growing, especially those of the genetic counseling and birth defects clinics. We need 1 or 2 (masters degree level) genetic associates for patient coordination, intake and routine genetic counseling (e.g. counseling of couples for prenatal diagnosis). Now, I am fully aware that we cannot ask N.I.H. for funds for clinical services, but there must be a way to divert activities of a small fraction of the total Genetic Center personnel to the clinical program. The equivalent of 1/4 - 1/2 time of a research assistant applied to performing enzyme assays for diagnostic purposes would meet our present needs. The annual salary of a genetics associate is about \$18,000 and 1/2 of this sum would provide considerable assistance to the clinical program. Help may be on its way from the U.S. government (genetic disease bill) but until help arrives (I have no idea of the timetable) is there no way of utilizing the Genetic Center for clinical genetics activities? There is precedent, of course, the GC/MS facilities are being used. I urge that these considerations enter into the design of the renewal application.

An appealing mix of projects with clinical collaboration and basic research projects which have the potential for leading to clinical innovation will require some budgetary innovations. The budget will have to be enlarged or (less desirable) budgetary limitations will have to be applied.

I have left the most difficult consideration for last. How is the effort (of the Genetic Center) different from a bunch of individual research grants. I'm not sure I can contribute creatively to this issue, so clear to the NIH administration. The easy, trite approach is to push interaction of the program-project people---seminars, meetings, collaboration, etc. This clearly has not worked in our "Genetics Center" so far. A common focus (such as gene mapping, genetics basis of mental illness, human immunogenetics) of the research projects in a program project grant probably justifies the Center approach over individual research efforts. Despite the title of Genetic Polymorphisms in Man, our "Center" has no common focus.

I am very attracted to your concept that this center should create an intellectual focus for (human) genetics in the medical school. To me this means that various faculty and investigators here should somehow be drawn to the activities of the Center, probably because these activities have something to offer, not necessarily research funds. Consultation is one such activity which could draw various workers to the "center". Rose Payne has always wanted genetic expertise for her HLA work and she has drawn on Walter Bodmer, Luca, Marc Feldman and me for consultation. Partial support from the "Genetic Center" makes it possible for me to provide consultation to the HLA group. I guess, Josh, interaction can be meaningful if all of us supported by the Center want to interact with each other and with other medical school colleagues with interests in common. A problem is that such interaction takes time and effort, perhaps more than any of us can give.

I cannot attend the August 25 faculty meeting. I am leaving for Europe on August 22 to attend the VII International Histocompatibility Workshop in Oxford (Walter is running the meeting). Thus, I have attempted to give you my thoughts about the renewal application in this long memo. I hope it will be helpful.